REMARKS

Examiner Interview on August 11, 2009

Applicant again thanks supervisory patent Examiner Ardin Marschel for taking the time to discuss the Office Action on August 11, 2009. Items discussed during the telephonic interview included the 35 USC § 103 claim rejections. Applicant re-explained that the prior art as a whole teaches away from a composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone, or other N-(substituted phenyl) pyridone compounds, as demonstrated by the issued claims of European Patent No. 0 702 551, and the Margolin Response dated October 1, 1999 submitted during the prosecution of European Patent No. 0 702 551 (copies of which were previously provided and are provided with this response). Examiner Marschel indicated that the response submitted by Applicant dated January 20, 2009 did not provide a copy of the Margolin Response dated October 1, 1999. As requested by the Examiner in order to assist in the consideration of Applicant's arguments, the following documents were provided to the Examiner on August 11, 2009:

- Exhibit A - a copy of the office action dated February 9, 1999 for European Patent No. 0 702 551;
- Exhibit B - the Margolin Response dated October 1, 1999 submitted during prosecution of European Patent No. 0 702 551;
- Exhibit C - a copy of European Patent No. 0 702 551.

Applicant directed the Examiner's attention to the office action for European Patent No. 0 702 551 dated April 4, 1999 under item 3, last paragraph, where the examiner stated "Unless the applicant can demonstrate a surprising effect, which does not appear from the application as filed, the subject-matter of claim 1-11 also lacks an inventive step." Applicant pointed out that Margolin's surprising effect is that "even minor structural changes from that of pirfenidone can significantly affect the properties as the results presented in the Table will demonstrate." (*see* Margolin response dated October 1, 1999).

Claim Status

Claim 29 is amended to define the two abbreviations that are used in the claim. Claim 26 is cancelled as it was not present in the previous listing of claims. This listing of claims will replace all prior versions, and listings of claims, in the application.

The amendments do not constitute an admission that the previously pending claims were anticipated, obvious, non-enabled, inadequately described or indefinite. Applicant reserves the right to file cancelled subject matter in a continuation or divisional application. Applicant respectfully requests reconsideration of the claims in light of the following arguments. Applicant believes that the Application is in a condition for allowance.

Claim Rejections: 35 U.S.C. § 112

In the Office Action of May 12, 2009, the Office rejected claim 29 under 35 U.S.C. § 112, second paragraph. It was alleged that the term "BHT" and "BHA" are unclear because there is no clear definition as to what BHT and BHA stand for.

Claim 29 is amended by stating the full meaning of the two abbreviations BHT and BHA, which are two antioxidants. Applicant respectfully requests that the rejection be withdrawn.

Claim Rejections: 35 U.S.C. § 103

Claims 4-6 and 11-12, 21-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,716,632 (Margolin) in view of U.S. Patent No. 3,839,346 (Gadekar) and Ansel et al. (Pharmaceutical dosage forms and drug delivery systems, Seventh edition, pages 87-92, Copyright 1999). For at least the following reasons, Applicant respectfully disagrees.

The Instant Claims

The instant claims are directed to a pharmaceutical composition comprising a N-(substituted phenyl) 2-(1H) pyridone compound of formula (I) and a pharmaceutically-acceptable excipient, where the 2-(1H) pyridone ring is substituted with R_1 and the phenyl is substituted with R_2, where R_2 is hydroxyl, sulfydryl, methylthio group, or ethylthio group at position 2, 3 or 4.

Teachings of the Prior Art

Per MPEP 2145(X)(D), "the prior art must be considered in its entirety, including disclosures that teach away from the claims." Further, per MPEP 2145(X)(D)(3) "the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of non-obviousness.'

U.S. Patent No. 5,716,632 (Margolin) and U.S. Patent No. 3,839,346 (Gadekar) disclose substituted 2-(1H)pyridone and substituted 3-(1H)pyridone compounds. European Patent No. 0 702 551, a European patent by Margolin, is directed to the same subject matter as described in U.S. Patent No. 5,716,632. European Patent No. 0 702 551 and its associated prosecution history teaches away from a pharmaceutical composition of 5-methyl-1-(4'-hydroxyphenyl)-2-(1H)

pyridone, or other N-(substituted phenyl) 2-(1H) pyridone compounds, as demonstrated by the issued claims of European Patent No. 0 702 551, and the Margolin Response dated October 1, 1999 submitted during the prosecution of European Patent No. 0 702 551.

Applicant directs the Examiner's attention again to the office action for European Patent No. 0 702 551 dated April 4, 1999 under item 3, last paragraph, where the European Examiner stated "Unless the applicant can demonstrate a surprising effect, which does not appear from the application as filed, the subject-matter of claim 1-11 also lacks an inventive step." Margolin's surprising effect is that "even minor structural changes from that of pirfenidone can significantly affect the properties as the results presented in the Table will demonstrate." (*see* Margolin response dated October 1, 1999). Margolin demonstrated that substitution on the phenyl ring of N-phenyl 2-(1H)pyridone compounds provides compounds that have **NO** antifibrotic activity.

Evidence of Unobviousness

"Unexpected property possessed by compound would be evidence of its unobviousness" (In re Wood 199 USPQ 137).

As stated above, the prior art provides objective evidence that N-(**substituted** phenyl) 2-(1H) pyridone compounds have no antifibrotic activity. As such, based on the teachings of the prior art, a person skilled in the art would not have been motivated to prepare a pharmaceutical composition of a compound that did not possess antifibrotic activity. Unexpectedly and contrary to accepted wisdom, N-(substituted phenyl) 2-(1H) pyridone compounds, where the phenyl is substituted with hydroxyl, sulfydryl, methylthio group, or ethylthio group at position 2, 3 or 4, do possess antifibrotic activity as demonstrated in the instant application. Therefore, a pharmaceutical composition of a N-(substituted phenyl) 2-(1H) pyridone compound, where the phenyl is substituted with hydroxyl, sulfydryl, methylthio group, or ethylthio group at position 2, 3 or 4 is unexpected and not obvious based on the teachings of the prior art.

Hydrogen and Methyl

The Office states that the prior art discloses the compound 5-methyl-1-(4'-methoxyphenyl)-2-(1H)pyridone and that the instant claims recite a hydroxy substituent on the phenyl instead of a methoxy substitutuent and that "hydrogen and methyl are deemed obvious variants" (In re Wood 199 USPQ 137). For at least three reasons, the Office does not properly cite In re Wood, in which a particular gem-dimethyl compound was found prima facie obvious over the unsubstituted analog.

First, in In re Wood, the prior art taught the unsubstituted compound and the new claim was directed to the gem-dimethyl analog – that is, the addition of a substituent. In the present case, the art teaches substitution, and the Examiner is arguing that removing the substitution is prima facie obvious, this 'reverse' use of In re Wood is not warranted by case law.

Second, in the present example, the prior art teaches methoxy (not methyl), and the present application claims hydroxy (not hydrogen). As is well known in the art, a methoxy group and a hydroxy group are substantially different groups: just compare dimethyl ether with ethanol, or anisole (methoxybenzene) with phenol. Very different compounds, with very different properties. The same would be expected in the present case.

Finally, the prior art specifically states that even subtle changes in the structure of these compounds provides unexpected/unpredictable activity relationships (*see* above). As a result, one of skill in the art would not be motivated to make the changes put forth by the Office.

Thus, the prior art provides objective evidence that N-(substituted phenyl) 2-(1H) pyridone compounds do not posses antifibrotic activity and teaches away from using N-(substituted phenyl) 2-(1H) pyridone compounds as antifibrotic compounds or incorporating N-(substituted phenyl) 2-(1H) pyridone compounds into pharmaceutical compositions. In light of the prior art as a whole and the fact that the presently claimed invention was derived contrary to accepted wisdom, Applicant asserts that the use of a N-(substituted phenyl) 2-(1H) pyridone compound in a *pharmaceutical* composition, where the phenyl is substituted with hydroxyl, sulfydryl, methylthio group, or ethylthio group at position 2, 3 or 4, is non-obvious. Thus, Applicant respectfully requests that the rejection be withdrawn.

Further Testing of Compounds Based on Prior Art

The Office also states in the Office Action dated May 12, 2009 on page 10 that "the official document of Margolin actually teaches a pharmaceutical composition of the instantly claimed drug and motivates an ordinarily skilled artisan to further test that composition." Applicant respectfully disagrees.

European Patent No. 0 702 551 and its associated prosecution history teaches away from a pharmaceutical composition that includes an N-(substituted phenyl) 2-(1H) pyridone compound. In fact, as stated above, the prior art as a whole teaches that N-(**unsubstituted** phenyl) 2-(1H) pyridone compounds have antifibrotic activity. Contrary to the interpretation of the prior art by the Office, an ordinarily skilled artisan **would not** be motivated to further test N-(**substituted** phenyl) 2-(1H)

pyridone compounds, which the prior art teaches **do not** have antifibrotic activity, but would be motivated to make and further test N-(**unsubstituted** phenyl) 2-(1H) pyridone compounds, which have been shown to have antifibrotic activity.

If the Office decides to maintain this position, then Applicant respectfully requests a clearer explanation as to why one or ordinary skill in the art would be motivated to disregard the teachings of the prior art and explore additional assays to further test compounds that are deemed inactive. The assay that was used by Margolin to test for antifibrotic activity indicates that it works well as evidenced by the biological results obtained for the N-(**unsubstituted** phenyl) 2-(1H) pyridone compounds, which were tested in the same manner as the 5-methyl-1-(4'-hydroxyphenyl)-2-(1H) pyridone compound.

Conclusion

In view of the forgoing arguments and objective evidence in the prior art and the instant application, Applicant assert that the instant claims are not obvious. Thus, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

Applicants submit that this response fully addresses the Office Action mailed May 12, 2009 and, that for the reasons set forth herein, the pending claims are in condition for allowance. This response is being filed with a three-month extension of time and a Request for Continued Examination (RCE) and the appropriate fees. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 34569-716.831).

Respectfully submitted,

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